Ritumab-500 Injection

DRUG INTERNATIONAL LTD.

Composition: Each vial (50ml) contains Rituximab INN 500mg (10mg/ml) solution for IV infusion.

Pharmacology: **Mechanism of Action:** Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Indications: • **Non–Hodgkin's Lymphoma (NHL):** Rituximab is indicated for the treatment of adult patients with: • Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent. • Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy. • Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy. • Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens. Rituximab is indicated for the treatment of pediatric patients aged 6 months and older with: • Previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in combination with chemotherapy.

• **Chronic Lymphocytic Leukemia (CLL):** Rituximab, in combination with fludarabine and cyclophosphamide (FC), is indicated for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.

• **Rheumatoid Arthritis (RA):** Rituximab, in combination with methotrexate, is indicated for the treatment of adult patients with moderately- to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

• **Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA):** Rituximab, in combination with glucocorticoids, is indicated for the treatment of adult and pediatric patients 2 years of age and older with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA).

• **Pemphigus Vulgaris (PV):** Rituximab is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris.

Dosage and Administration: **Administration only as an Intravenous Infusion:** It should not be administered as an intravenous push or bolus. Rituximab should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur. It should be premedicated before each infusion. Or, as directed by the registered physicians.

• **First Infusion:** Standard Infusion: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. For Pediatric Patients with mature B-cell NHL/B-AL: Initiate infusion at a rate of 0.5 mg/kg/hr (maximum 50 mg/hr). In the absence of infusion toxicity, increase infusion rate by 0.5 mg/kg/hr every 30 minutes, to a maximum of 400 mg/hr. • **Subsequent Infusions:** Standard Infusion: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr. For Previously Untreated Follicular NHL and DLBCL adult patients: If patients did not experience a Grade 3 or 4 infusion-related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen. Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8). Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count greater than or equal to 5,000/mm3 before Cycle 2 should not be administered the 90-minute infusion.

• **Recommended Dose for Non-Hodgkin's Lymphoma (NHL):** The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules: • **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL:** It should be administered once weekly for 4 or 8 doses. • **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL:** It should be administered once weekly for 4 doses.

• **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL:** It should be administered on Day 1 of each cycle of chemotherapy for up to 8 doses. In patients with complete or partial response, initiate Rituximab maintenance eight weeks following completion of a rituximab product in combination with chemotherapy. It should be administered as a single-agent every 8 weeks for 12 doses. • **Non-progressing, Low-Grade, CD20-Positive, B-Cell NHL, after first-line CVP chemotherapy:** Following completion of 6–8 cycles of CVP chemotherapy, It should be administered once weekly for 4 doses at 6-month intervals to a maximum of 16 doses. • **Diffuse Large B-Cell NHL:** It should be administered on Day 1 of each cycle of chemotherapy for up to 8 infusions. • **Pediatric patients aged 6 months and older with previously untreated mature B-cell NHL/B-AL:** Rituximab is given in combination with systemic Lymphome Malin B (LMB) chemotherapy. In total, six infusions of Rituximab are given, two doses during each of the induction courses, COPDAM1 and COPDAM2, and one dose during each of the two consolidation courses of CYM/CYVE.

• **Recommended Dose for Chronic Lymphocytic Leukemia (CLL):** The recommended dose is 375 mg/m^2 the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on Day 1 of cycles 2–6 (every 28 days).

• **Recommended Dose for Rheumatoid Arthritis (RA):** • Rituximab should be administered as two-1,000 mg intravenous infusions separated by 2 weeks. • Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion-related reactions. • Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. • Rituximab is given in combination with methotrexate.

• **Recommended Dose for Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA):** • Rituximab should be administered as a 375 mg/m^2 intravenous infusion once weekly for 4 weeks for patients with active GPA or MPA. • Glucocorticoids administered as methylprednisolone 1,000 mg intravenously per day for 1 to 3 days followed by oral prednisone as per clinical practice. This regimen should begin within 14 days prior to or with the initiation of Rituximab and may continue during and after the 4 week induction course of Rituximab treatment.

Recommended Dose for Pemphigus Vulgaris (PV): • Rituximab should be administered as two-1,000 mg intravenous infusions separated by 2 weeks in combination with a tapering course of glucocorticoids. • **Maintenance treatment:** Rituximab should be administered as a 500 mg intravenous infusion at Month 12 and every 6 months thereafter or based on clinical evaluation. •**Treatment of relapse:** Rituximab should be administered as a 1,000 mg intravenous infusion on relapse, and consider resuming or increasing the glucocorticoid dose based on clinical evaluation. Subsequent infusions of Rituximab may be administered no sooner than 16 weeks following the previous infusion.

PREPARATION FOR ADMINISTRATION

Appropriate aseptic technique should be used. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. The vial should not be used it particulates or discoloration is present. Necessary amount of Rituximab should be withdrawn from vial and diluted to a final concentration of 1 mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in water USP. The bag should be gently inverted to mix the solution, should not be mixed or diluted with other drugs. Any unused portion left in the vial should be discarded.

However, since Rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C to 8°C). No incompatibilities between Rituximab and polyvinylchloride or polyethylene bags have been observed.

Contraindications: It is contraindicated in patients with known hypersensitivity to Rituximab or any other components of this product.

Precautions: **Infusion-Related Reactions:** Rituximab can cause severe, including fatal, infusion-related reactions. Rituximab -induced infusion-related reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. For pediatric patients with mature B-cell NHL/B-AL, prednisone should be administerd as part of chemotherapy regimen prior to Rituximab during induction and as needed for subsequent cycles. **Severe Mucocutaneous Reactions:** Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of Rituximab exposure. Rituximab should be discontinued in patients who experience a severe mucocutaneous reaction. **Progressive Multifocal Leukoencephalopathy (PML):** The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Rituximab should be discontinued and considered discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML. **Tumor Lysis Syndrome (TLS):** It should be administered aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administered supportive care, including dialysis as indicated. **Infections:** Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of Rituximab-based therapy. Rituximab should be discontinued for serious infections and institute appropriate anti-infective therapy. Rituximab is not recommended for use in patients with severe, active infections.

Side Effects: The most common side effects are • Infusion-related reactions • Severe mucocutaneous reactions • Hepatitis B reactivation with fulminant hepatitis • Progressive multifocal leukoencephalopathy • Tumor lysis syndrome • Infections • Cardiovascular adverse reactions • Renal toxicity • Bowel obstruction and perforation.

Use in Pregnancy and Lactation: Rituximab can cause fetal harm when administered to a pregnant woman. Rituximab can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed to Rituximab in-utero. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated populations is unknown. **Lactation:** There are limited data on the presence of Rituximab in human milk and the effect on the breastfed child, and there are no data on the effect on milk production. Rituximab has also been reported to be excreted at low concentrations in human breast milk. Given that the clinical significance of this finding for children is not known, Women should not be advised to breastfeed during treatment with Rituximab and for 6 months after the last dose due to the potential of serious adverse reactions in breastfed children.

Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating Rituximab. **Contraception: Females:** Females should be advised of reproductive potential to use effective contraception during treatment with Rituximab and for 12 months after the last dose.

Pediatric Use: Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA): Rituximab is not indicated in pediatric patients less than 2 years of age with GPA or MPA. **Mature B-Cell NHL/B-AL:** The safety and effectiveness of Rituximab in combination with chemotherapy for the treatment of previously untreated, advanced stage, CD20-positive DLBCL/BL/BLL/B-AL have been established in pediatric patients aged 6 months and older. **Rheumatoid Arthritis and Pemphigus Vulgaris:** The safety and effectiveness of Rituximab have not been established in pediatric patients with PVor RA. Rituximab was not studied in pediatric patients with polyarticular juvenile idiopathic arthritis (PJIA) due to concerns regarding the potential for prolonged immunosuppression as a result of B-cell depletion in the developing juvenile immune system.

Drug Interactions: Formal drug interaction studies have not been performed with Rituximab. In patients with CLL, Rituximab did not alter systemic exposure to fludarabine or cyclophosphamide.

Overdose: Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

Storage: Store the vial in original carton at 2°C-8°C in a refrigerator. Do not freeze. Protect from light. Keep out of the reach of children.

Packaging: Each box contains one vial of 50ml sterile solution of Rituximab 500mg for IV infusion.